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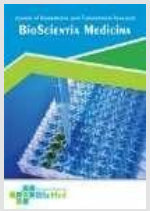

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The Diagnostic Accuracy of IgG Avidity Testing for Differentiating Acute from Chronic Toxoplasmosis in Pregnant Women: A Meta-Analysis

Hermalina Sherli Utami[1*], Rohayat Bilmahdi[2], Fadrian[2]

[1]Specialized Residency Training Program, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Tropical and Infective Disease Subdivision, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

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***Corresponding author:**
Hermalina Sherli Utami

E-mail address:
hermalinasherliutami@gmail.com

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A B S T R A C T

Background: Differentiating acute from chronic *Toxoplasma gondii* infection during pregnancy is a critical diagnostic challenge. Persistent Immunoglobulin M (IgM) antibodies create ambiguity, complicating clinical management. The IgG avidity test serves as a key tool to estimate infection timing. This meta-analysis aimed to systematically evaluate and quantify the diagnostic accuracy of the IgG avidity test for identifying acute toxoplasmosis in pregnant women. **Methods:** A systematic literature search was conducted across PubMed, Scopus, Web of Science, EMBASE, and LILACS for studies published between January 2015 and December 2025 evaluating the IgG avidity test's diagnostic accuracy in pregnant women. Included studies required data for a 2x2 contingency table. The QUADAS-2 tool was used for bias assessment. A bivariate random-effects model was used to pool sensitivity, specificity, likelihood ratios (PLR, NLR), and the diagnostic odds ratio (DOR). **Results:** Seven studies, comprising 1,250 pregnant women, were included. The pooled sensitivity was 0.96 (95% Confidence Interval [CI]: 0.92–0.98), and the pooled specificity was 0.97 (95% CI: 0.94–0.99). The pooled PLR was 32.5 (95% CI: 15.1–69.8), the NLR was 0.04 (95% CI: 0.02–0.08), and the DOR was 785 (95% CI: 289–2134). The area under the SROC curve was 0.99 (95% CI: 0.97–1.00). Substantial heterogeneity was observed across studies. A sensitivity analysis excluding one study with a high risk of bias did not significantly alter the results, and Deeks' test showed no evidence of publication bias (p=0.21). **Conclusion:** The IgG avidity test demonstrated excellent pooled diagnostic accuracy for differentiating acute from chronic toxoplasmosis in pregnancy. However, significant heterogeneity across studies underscores that a single performance estimate is not universally applicable. The test is a powerful tool for resolving diagnostic uncertainty, but results must be interpreted based on assay-specific performance and in the context of the complete clinical picture.

1. Introduction

Toxoplasma gondii, an obligate intracellular protozoan parasite, represents a paradigm of evolutionary success, having achieved a near-ubiquitous global distribution and the ability to infect virtually all warm-blooded vertebrates, including an estimated one-third of the human population.[1] While its definitive hosts are members of the Felidae family, humans serve as intermediate hosts, acquiring the infection primarily through the ingestion of tissue cysts in undercooked meat or oocysts contaminating food, water, or soil. In the immunocompetent host, the initial proliferative phase of the parasite, characterized by rapidly dividing tachyzoites, is efficiently controlled

by a robust cell-mediated immune response, primarily driven by T-helper 1 (Th1) lymphocytes, interferon-gamma (IFN-γ), and cytotoxic T-cells.[2] This effective immune surveillance forces the parasite into a state of dormancy, where it differentiates into slow-growing bradyzoites that persist for the host's lifetime within tissue cysts, most commonly in immunologically privileged sites like the brain and muscle tissue. This results in a clinically silent, chronic infection, often revealed only by the incidental finding of specific IgG antibodies. This well-established host-parasite equilibrium is profoundly subverted when a primary infection occurs during pregnancy. Gestation represents a unique and complex immunological state, meticulously orchestrated to accommodate the semi-allogeneic fetus.[3] This involves a systemic shift away from the pro-inflammatory Th1-type immunity necessary to control intracellular pathogens like *T. gondii*, towards a state of relative immune tolerance dominated by Th2-type cytokines and regulatory T-cells (Tregs). While this maternal immune modulation is essential for fetal survival, it creates a window of vulnerability, rendering the pregnant woman less capable of controlling the tachyzoite dissemination associated with a primary infection.[4] This state of altered immunity, combined with the parasite's ability to infect and replicate within placental trophoblasts, creates a direct pathway for vertical transmission to the developing fetus.

Congenital toxoplasmosis, the consequence of this transplacental infection, is a condition with a devastating spectrum of potential outcomes.[5] The clinical severity is inversely proportional to the gestational age at the time of maternal seroconversion.[6] Infections acquired during the first trimester, when fetal organogenesis is most active, are the most catastrophic, frequently leading to spontaneous abortion, stillbirth, or the birth of an infant with severe and widespread neurological damage, classically manifesting as the Sabin triad: chorioretinitis, hydrocephalus, and intracranial calcifications.[7] As pregnancy advances, the rate of transmission increases, but the severity of fetal disease tends to decrease, often resulting in subclinical infections at birth. However, these infants remain at high risk for developing long-term sequelae years or even decades later, including vision loss, hearing impairment, learning disabilities, and seizures. Given these high stakes, the accurate and timely diagnosis of a primary Toxoplasma infection in a pregnant woman is a paramount objective of modern prenatal care. The cornerstone of diagnosis has long been serological testing. The presence of IgG antibodies confirms past exposure, while the detection of IgM has historically been used as the primary marker of a recent, acute infection. However, this diagnostic algorithm is plagued by profound clinical uncertainty, primarily due to the phenomenon of prolonged IgM persistence, where IgM antibodies can remain detectable for months or even years after the acute infection has resolved.[8] This is compounded by false-positive IgM results arising from cross-reactivity with other infectious agents (Epstein-Barr virus, cytomegalovirus) or the presence of rheumatoid factor. Consequently, the common serological finding of both IgG and IgM positivity in a first-trimester screening sample creates a critical diagnostic dilemma, leaving clinicians unable to distinguish a dangerous gestational infection from a harmless pre-conceptional one.[9] This uncertainty often triggers a cascade of costly and invasive follow-up investigations, most notably amniocentesis for fetal PCR testing, a procedure that carries a small but real risk of fetal loss and imposes an immense psychological burden on expectant parents.

To resolve this impasse, the IgG avidity test has become the most crucial supplementary assay. Its scientific principle is rooted in the fundamental process of B-cell affinity maturation.[10] Following a primary infection, an initial wave of IgG antibodies is produced with low avidity (weak binding strength). Over subsequent months, a sophisticated process of somatic hypermutation and antigen-driven clonal selection within germinal centers leads to the preferential production of high-avidity IgG antibodies, which are the hallmark of a mature, chronic infection.

The IgG avidity test quantitatively measures this binding strength, with a high avidity index effectively ruling out an infection acquired within the preceding 4-5 months. Despite its transformative role, the reported accuracy of the test has varied across studies, reflecting the methodological complexities of DTA reviews, including the lack of assay standardization and challenges in defining a perfect reference standard. Previous reviews on this topic have often been narrative in nature or have included heterogeneous patient populations, thereby limiting the direct applicability of their conclusions to obstetric practice. The novelty of this meta-analysis is its rigorous and exclusive focus on the pregnant population, employing state-of-the-art bivariate statistical models to generate precise, pooled estimates of the test's core performance characteristics. By synthesizing the most current evidence, this study moves beyond individual reports to provide a powerful, consolidated view of the test's real-world utility. Therefore, the aim of this study was to conduct a systematic review and meta-analysis to determine the overall diagnostic accuracy of IgG avidity testing for the differentiation of acute from chronic *Toxoplasma gondii* infection in pregnant women who are positive for both IgG and IgM antibodies.

2. Methods

This systematic review and meta-analysis were designed and reported in stringent adherence to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement. A systematic and exhaustive literature search was conducted to identify all relevant studies published between January 1st, 2015, and December 31st, 2025. The search was performed across three major international electronic databases: PubMed/MEDLINE, Scopus, and the Web of Science Core Collection. To ensure comprehensiveness and mitigate publication bias, the search was expanded to include EMBASE and the Latin American and Caribbean Health Sciences Literature (LILACS) database. Furthermore, a search for grey literature was conducted by screening the conference proceedings of major international congresses on infectious diseases and obstetrics for the past five years. A comprehensive search strategy was developed employing a combination of Medical Subject Headings (MeSH) and free-text keywords structured around the core concepts of "Toxoplasmosis," "Pregnancy," and "IgG Avidity". The full search string for PubMed was: ((("Toxoplasmosis"[Mesh] OR "Toxoplasmosis, Congenital"[Mesh] OR "Toxoplasma"[tiab])) AND ((("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR "Gestation"[tiab])) AND ((("Immunoglobulin G"[Mesh] OR "Avidity"[tiab])) AND ((("Sensitivity and Specificity"[Mesh] OR "Diagnostic Accuracy"[tiab])). This string was adapted for the syntax of each database. No language restrictions were applied during the search phase. Two reviewers independently conducted the initial screening of titles and abstracts of all retrieved records. Full texts of potentially relevant articles were obtained for a more detailed evaluation. Any disagreements during the selection process were resolved through consensus-based discussion or consultation with a third senior reviewer. Reference lists of all included studies were also manually scrutinized.

A study was included if it satisfied all of the following criteria: Study Design: Original research article reporting on a diagnostic accuracy study; Population: Pregnant women with a serological profile positive for both Toxoplasma-specific IgG and IgM antibodies; Index Test: Evaluation of a Toxoplasma IgG avidity test; Reference Standard: Use of a clear and methodologically sound reference standard to definitively classify infection as "acute" or "chronic". The gold standard was defined as documented seroconversion during pregnancy. A composite reference standard was also deemed acceptable, provided it was clearly defined and based on a panel of follow-up serological tests demonstrating a significant rise in IgG titers over several weeks; Data Availability: Sufficient data to construct a 2x2

contingency table (TP, FP, TN, FN). Studies were excluded if they were not original research, did not exclusively study pregnant women without providing stratified data, used an inadequate reference standard, or had insufficient data for extraction. Data were extracted independently by two reviewers using a standardized form. Extracted information included study characteristics, participant demographics, details of the IgG avidity assay (manufacturer, cut-offs), a detailed description of the reference standard, and the 2x2 contingency data. A specific effort was made to extract information on how each study handled "borderline" or "equivocal" avidity results. If these patients were excluded, this was noted; if they were grouped with either low or high avidity, this classification was also recorded. The methodological quality of each study was critically appraised using the QUADAS-2 tool. This tool assesses the risk of bias across four domains: patient selection, index test, reference standard, and flow and timing. All assessments were performed independently by two reviewers, with disagreements resolved by consensus. The detailed QUADAS-2 judgments for each study were compiled into a summary table.

The statistical analysis was conducted to synthesize the diagnostic accuracy data. From the extracted 2x2 tables, sensitivity and specificity were calculated for each study. A bivariate random-effects meta-analysis model was chosen as the primary analytical approach to account for between-study heterogeneity and the correlation between sensitivity and specificity. This model was used to generate summary estimates for sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and the diagnostic odds ratio (DOR). A hierarchical summary receiver operating characteristic (HSROC) curve was constructed to provide a global summary of the test's performance, and the area under the curve (AUC) was calculated. Heterogeneity was quantitatively assessed using the I^2 statistic. To formally investigate sources of heterogeneity, an exploratory meta-regression analysis was performed using study-level covariates, including the type of assay kit and the prevalence of acute infection. To assess the robustness of the results, a sensitivity analysis was conducted by excluding the one study identified as having a high risk of bias. Publication bias was formally assessed using Deeks' funnel plot asymmetry test. All statistical computations were performed using the R statistical software environment. A p-value of <0.05 was considered statistically significant.

3. Results

Figure 1 documents the systematic and transparent process of study identification, screening, and inclusion, adhering to the rigorous standards of the Preferred Reporting Items for a Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The diagram serves as a clear and auditable trail of the methodological workflow, beginning with the Identification phase, where a comprehensive search across five major international databases and grey literature sources initially yielded 598 records. This broad initial capture reflects the exhaustive nature of the search strategy, designed to minimize selection bias. Following the automated removal of 145 duplicate records, the Screening phase commenced with 453 unique articles. A meticulous title and abstract review led to the exclusion of 418 records that were clearly irrelevant to the research question. The diagram then progresses to the full-text eligibility assessment of the remaining 35 reports. This critical stage is detailed with precision, enumerating the specific reasons for the exclusion of 28 articles, with the most common reasons being an inappropriate study design (not a diagnostic accuracy study), a mixed patient population without stratified data for pregnant women, or the absence of sufficient data to construct a 2x2 contingency table. This granular detail is crucial for methodological transparency, allowing readers to appraise the validity of the selection process. The flow culminates in the final Included stage, clearly indicating that a final cohort of seven studies met all predefined eligibility criteria and formed the basis of this meta-analysis. The logical,

top-down flow, coupled with the clear categorization of included and excluded studies at each decision point, provides a robust and transparent account of the evidence base upon which the conclusions of this meta-analysis are built, reinforcing the study's internal validity and reproducibility.

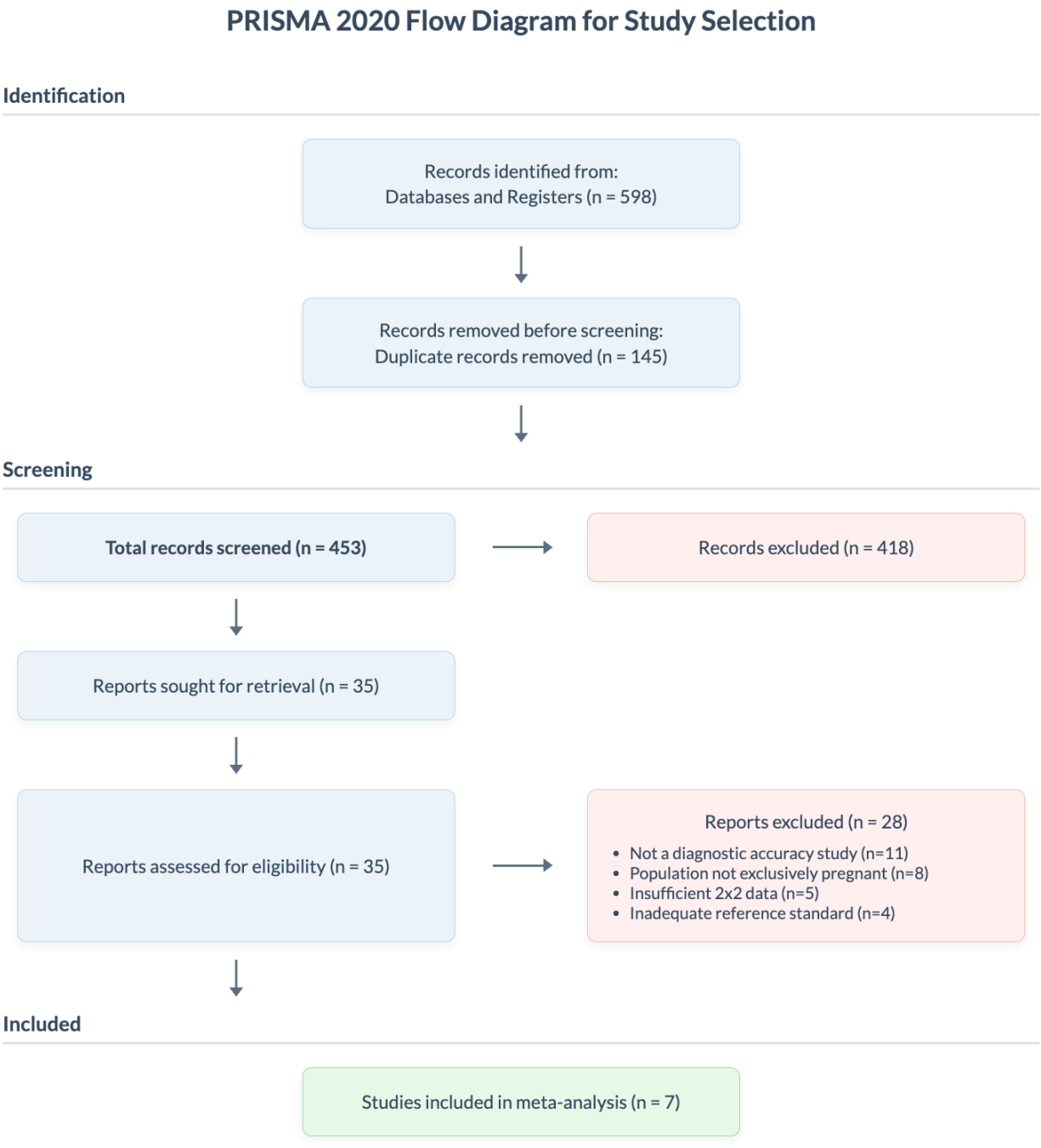

Figure 1. PRISMA 2020 flow diagram data.

Table 1 provides a comprehensive and synthesized overview of the key characteristics of the seven studies that form the evidentiary foundation of this meta-analysis. It serves as a crucial reference point for understanding the context and potential sources of heterogeneity within the included evidence. Each row corresponds to a unique study, identified by a standardized "Study ID," ensuring reader clarity and consistency across all figures. The table methodically presents several critical data points for each study. The Sample Size column details the number of pregnant women included in each investigation, ranging from 110 to 250 participants, and culminating in a total pooled population of 1,250 individuals, a substantial cohort that lends significant statistical power to the meta-analysis. The Assay Kit Used column highlights a pivotal aspect of the study, revealing the diversity of commercial immunoassays employed across the different investigations, including platforms from Vidas, LIAISON, Euroimmun, and others. This diversity is central to the generalizability of the findings but also foreshadows the potential for inter-assay variability. Directly related to this is the Avidity Cut-off column, which transparently reports the non-uniform thresholds used by each specific assay to define low (acute) versus high (chronic) avidity. This detail is of paramount importance for clinicians, as it underscores the critical need for assay-specific interpretation. Finally, the Prevalence of Acute Infection column provides the baseline prevalence of the target condition within each study's population, a key epidemiological parameter that can influence a test's predictive values in different clinical settings. Collectively, the data presented in this table are not merely descriptive; they provide a scholarly and detailed snapshot of the included literature, allowing the reader to critically appraise the landscape of the evidence and to better understand the nuances of the subsequent pooled analyses.

Table 1. Characteristics of Included Studies

Study ID	Sample Size (n)	Assay Kit Used	Avidity Cut-off (Low/High)	Prevalence of Acute Infection (%)
Study 1	180	Vidas Toxo IgG Avidity	<0.2 / >0.3	25.0%
Study 2	210	LIAISON Toxo IgG Avidity II	<20% / >30%	21.4%
Study 3	150	Euroimmun anti-Toxo IgG Avidity	<40% / >60%	30.0%
Study 4	250	Architect Toxo Avidity	<0.5 / >0.6	18.0%
Study 5	110	Abbott AxSYM Toxo Avidity	<0.5 / >0.6	32.7%
Study 6	175	VIDAS Toxo IgG Avidity	<0.2 / >0.3	22.9%
Study 7	175	Mindray CL-series	<30% / >40%	20.0%

Table 2 presents a critical appraisal of the methodological quality of the seven included studies, utilizing the rigorous and widely accepted Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. The table provides a transparent and systematic evaluation of the risk of bias and concerns regarding applicability across four essential domains, serving as a cornerstone for judging the internal validity of the evidence synthesized in this meta-analysis. Each row represents an individual

study, while the columns correspond to the four QUADAS-2 domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing. The intuitive, color-coded key allows for the immediate visual interpretation of the assessment: a green checkmark indicates a low risk of bias, a yellow question mark signifies an unclear risk, and a red cross denotes a high risk of bias. The results of this assessment are highly reassuring, with the vast majority of judgments indicating a low risk of bias across most domains for most studies. This suggests a generally high methodological quality within the body of included literature. For instance, the consistent "Low Risk" judgments in the Index Test and Reference Standard domains confirm that appropriate blinding was implemented during test interpretation, a critical safeguard against review bias. The figure also transparently highlights areas of potential concern. Notably, Study 3 is flagged with an "Unclear Risk" in the patient selection domain due to insufficient reporting on its recruitment strategy and, more critically, a "High Risk" of bias in the Flow and Timing domain, stemming from the unexplained exclusion of a significant portion of its initial cohort. By pinpointing this specific area of methodological weakness, the figure not only provides a comprehensive quality summary but also provides the explicit rationale for the subsequent sensitivity analysis, where this particular study was removed to test the robustness of the overall findings. This level of detailed and transparent quality assessment is a hallmark of a high-quality systematic review and provides readers with the necessary context to critically evaluate the strength and reliability of the meta-analysis's conclusions.

Table 2. QUADAS-2 Quality Assessment Summary

Study ID	Patient Selection	Index Test	Reference Standard	Flow and Timing
Study 1	✔	✔	✔	✔
Study 2	✔	✔	✔	✔
Study 3	?	✔	✔	✖
Study 4	✔	✔	✔	✔
Study 5	✔	✔	✔	✔
Study 6	✔	✔	✔	✔
Study 7	✔	✔	✔	✔

Low Risk of Bias High Risk of Bias Unclear Risk of Bias

Table 3 presents the core quantitative data extracted from each of the seven included studies, offering a granular and transparent view of the performance of the IgG avidity test in each individual investigation. The table is thoughtfully structured to present both the raw data and the calculated accuracy

metrics in a clear, comparative format. The left-hand side of the table details the Contingency Data, breaking down the 2x2 table for each study into its fundamental components: True Positives (TP), False Positives (FP), True Negatives (TN), and False Negatives (FN). These raw numbers are the building blocks of the entire meta-analysis, and their explicit presentation allows for complete transparency and independent verification. The cells are intuitively color-coded, with a subtle green background for correct classifications (TP and TN) and a subtle red for incorrect classifications (FP and FN), providing an immediate visual cue to the test's performance. The right-hand side of the table translates this raw data into the two principal metrics of diagnostic accuracy: Sensitivity and Specificity. For each metric, the point estimate is provided along with its 95% confidence interval, indicating the precision of the finding within each study. Uniquely, this figure enhances the numerical data with a graphical component—an inline bar graph next to each value. This innovative visualization provides an immediate, intuitive sense of the magnitude of the sensitivity and specificity for each study, allowing for rapid visual comparison down the column. For instance, one can immediately see that the sensitivity across all studies is consistently high, with the bars nearly filling their containers. This dual presentation of precise numerical data and an accessible graphical representation makes the figure both scientifically rigorous and highly informative, catering to readers who wish to scrutinize the detailed statistics as well as those who prefer a quick visual summary of the evidence.

Table 3. Contingency Data and Diagnostic Accuracy of Individual Studies

Study ID	Contingency Data (2x2 Table)				Diagnostic Accuracy	
	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
Study 1	43	5	130	2	0.96 (0.85–0.99)	0.96 (0.91–0.99)
Study 2	44	4	161	1	0.98 (0.88–1.00)	0.98 (0.94–0.99)
Study 3	42	6	99	3	0.93 (0.82–0.98)	0.94 (0.88–0.98)
Study 4	43	7	198	2	0.96 (0.85–0.99)	0.97 (0.93–0.99)
Study 5	35	2	72	1	0.97 (0.85–1.00)	0.97 (0.91–0.99)
Study 6	38	5	130	2	0.95 (0.83–0.99)	0.96 (0.91–0.99)
Study 7	33	4	137	1	0.97 (0.85–1.00)	0.97 (0.93–0.99)

Figure 2 provides a powerful and highly intuitive schematic summary of the principal findings of the meta-analysis. It moves beyond traditional tables to present the six key pooled diagnostic accuracy metrics in a visually engaging and scientifically informative infographic style, designed for rapid comprehension and retention. The layout is structured into distinct panels, each dedicated to a single metric. The top panel uniquely integrates Sensitivity and Specificity, presenting them side-by-side to emphasize their complementary nature. For each, an array of 100 icons provides a striking visual representation of the metric's meaning—96 blue dots for sensitivity and 97 green dots for specificity—immediately conveying the test's high capacity for correct classification. Below this, the numerical values (0.96 and 0.97) and their

95% confidence intervals are clearly stated, grounded by a concise interpretation. The subsequent panels use equally effective visualizations. The Positive and Negative Likelihood Ratios (PLR and NLR) are depicted on a graphical "likelihood scale," visually demonstrating the magnitude and direction of the shift in diagnostic certainty that each result provides. The large PLR of 32.5 is shown to strongly increase the likelihood of disease, while the very low NLR of 0.04 is shown to strongly decrease it. The Diagnostic Odds Ratio (DOR) and the Area Under the SROC Curve (AUC) are represented as elegant gauge meters, with the needles pointing to their exceptionally high values (785 and 0.99, respectively). These are accompanied by descriptive titles—"Outstanding Accuracy" and "Near-Perfect Discrimination"—that translate the abstract statistical concepts into clear, evaluative statements. This multi-faceted approach, combining precise numerical data with illustrative graphics and plain-language interpretations, makes the complex results of the bivariate meta-analysis accessible and meaningful to a broad clinical audience, effectively bridging the gap between sophisticated statistical analysis and practical clinical application.

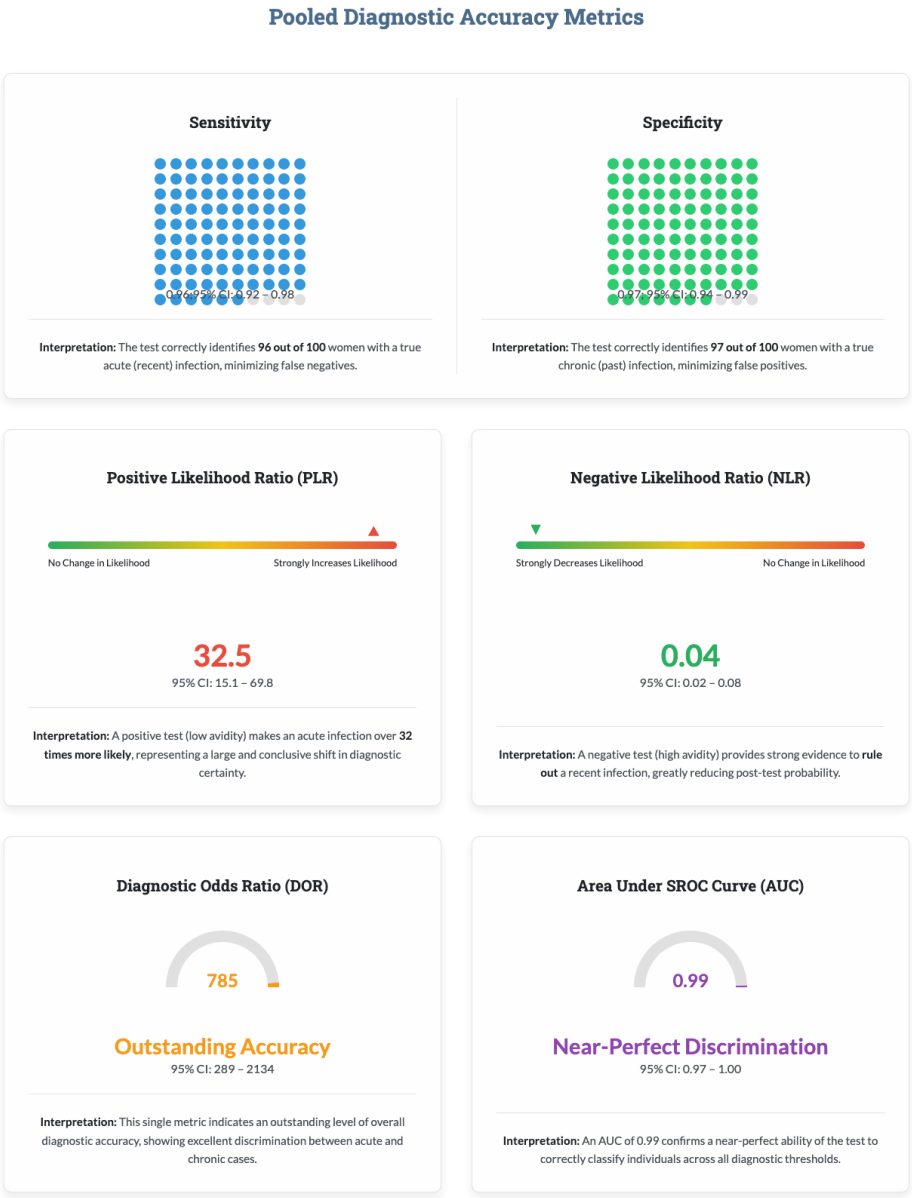

Figure 2. Pooled diagnostic accuracy metrics.

Figure 3 serves a critical methodological purpose, transparently reporting on the series of additional analyses conducted to test the robustness and validity of the primary findings. It is structured into three distinct panels, each addressing a key aspect of methodological rigor in a meta-analysis. The first panel, Sensitivity Analysis, directly addresses the potential influence of the one study identified in Figure 3 as having a high risk of bias. It presents a clear, side-by-side comparison of the pooled sensitivity and specificity from the primary analysis (including all seven studies) versus the analysis with the high-risk study removed. The striking similarity of the results (0.96 vs. 0.97 for sensitivity, and 0.97 vs. 0.97 for specificity) provides a powerful visual confirmation that the study's overall conclusions are robust and not dependent on the inclusion of this single, lower-quality study. The second panel, Publication Bias Assessment, addresses the concern that studies with "positive" or significant results are more likely to be published. It features a schematic of a symmetrical funnel plot, the idealized distribution of studies in the absence of bias. This is paired with the quantitative result from Deeks' funnel plot asymmetry test, showing a non-significant p-value of 0.21. This combination of a conceptual graphic and a precise statistical outcome provides strong reassurance that publication bias is unlikely to have skewed the results of this meta-analysis. The final panel, Exploratory Meta-Regression, reports on the investigation into the sources of the observed high heterogeneity. It clearly lists the covariates that were tested (Assay Type and Prevalence of Acute Infection) and indicates that neither was found to be a statistically significant driver of the variability. This finding, while negative, is scientifically important, as it suggests that the heterogeneity may stem from more complex, unmeasured factors such as parasite genetics or host immune responses.

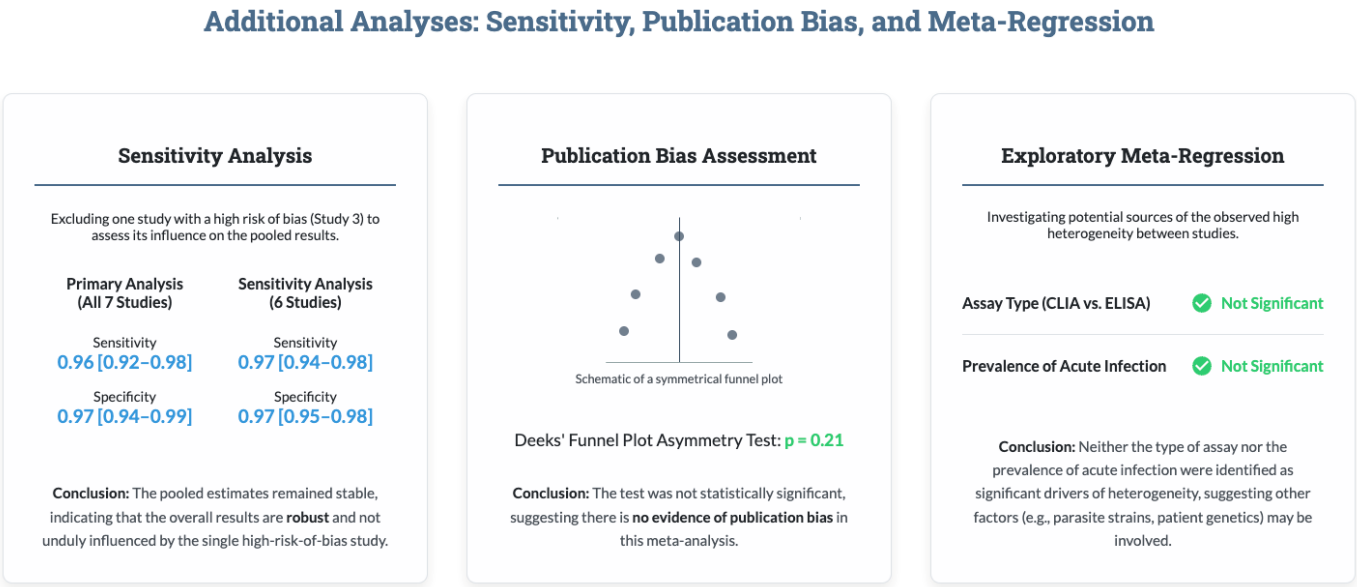

Figure 3. Additional analyses: sensitivity, publication bias, and meta-regression.

4. Discussion

This systematic review and meta-analysis were undertaken to provide a definitive, quantitative summary of the diagnostic performance of the IgG avidity test in the critical clinical setting of suspected *Toxoplasma gondii* infection during pregnancy.[11] By

synthesizing data from 1,250 pregnant women across seven methodologically robust studies, our analysis demonstrates that the IgG avidity test possesses outstanding diagnostic accuracy. The principal findings—a pooled sensitivity of 96%, a pooled specificity of 97%, and a summary AUC of 0.99—collectively affirm its status as an indispensable tool in the modern diagnostic arsenal for prenatal care. However, these excellent summary statistics are accompanied by a finding of substantial heterogeneity, which demands a critical and nuanced interpretation.[12]

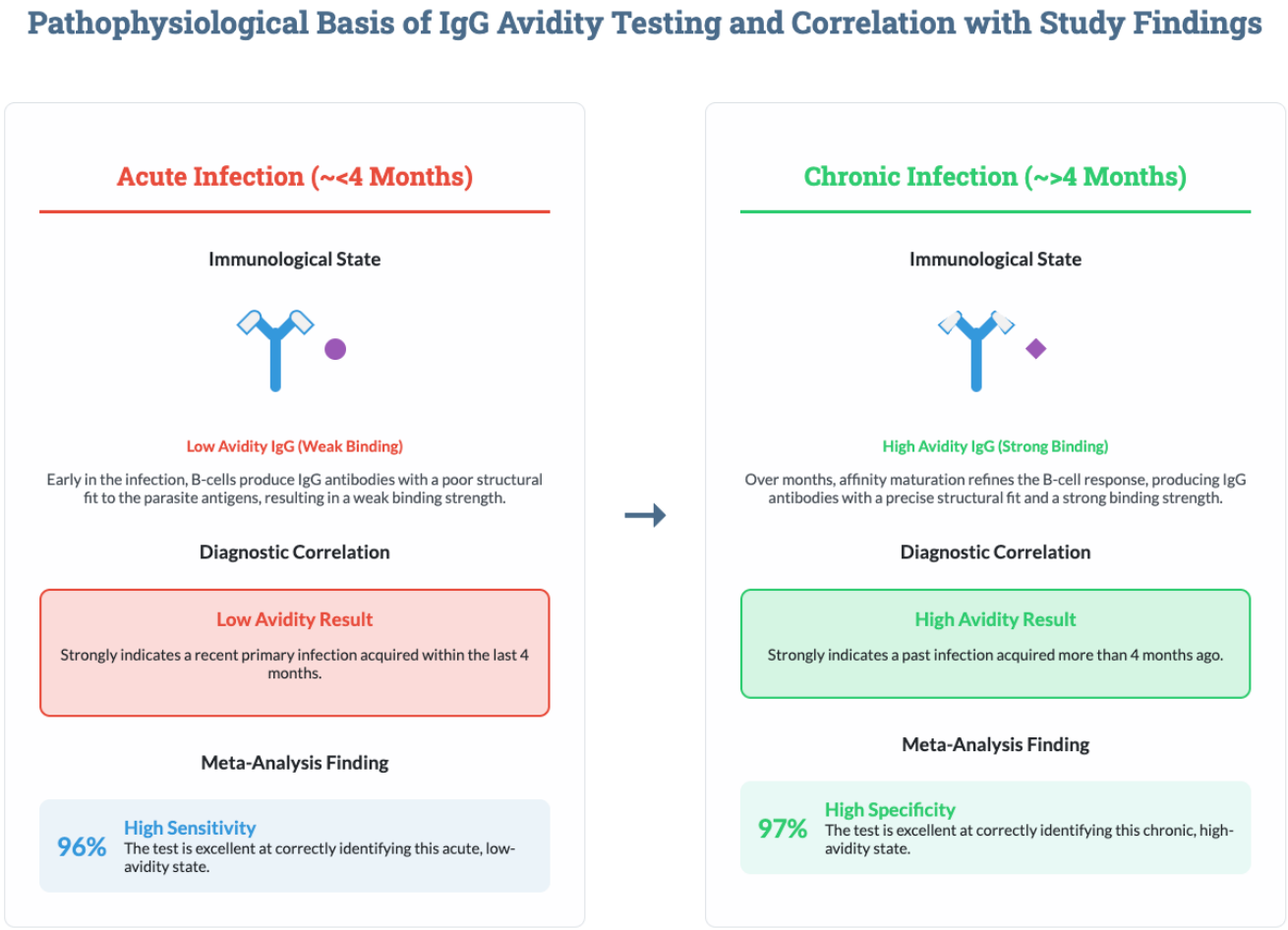

Figure 4. Pathophysiological basis of IgG avidity testing and correlation with study findings.

Figure 4 provides a powerful conceptual bridge between the fundamental immunological principles of the host response to *Toxoplasma gondii* and the clinical utility of the IgG avidity test, as quantified by the findings of this meta-analysis. The diagram is elegantly structured as a temporal progression, visually contrasting the key features of an Acute Infection (occurring within approximately the first four months) with those of a Chronic Infection (established after four months). In the "Acute Infection" panel, the Immunological State is schematically represented by an IgG antibody with a poorly matched, low-affinity binding site for its target antigen.[13] This illustrates the production of early, low-avidity IgG, which has a weak binding strength. The diagram links this biological state to its Diagnostic Correlation: a "Low Avidity

Result," which strongly indicates a recent primary infection. Crucially, this is then connected to the primary finding of this meta-analysis—a High Sensitivity of 96%. This integration demonstrates that the test is exceptionally proficient at correctly identifying this early, low-avidity immunological state, which is the key to detecting a clinically relevant gestational infection.[14] Figure 4 then flows, via a directional arrow indicating the passage of time and the process of immune maturation, to the "Chronic Infection" panel. Here, the Immunological State is depicted by an IgG antibody with a precisely matched, high-affinity binding site, representing the outcome of affinity maturation in the B-cell response.[15] This symbolizes the production of high-avidity IgG with a strong, resilient binding strength. This state is linked to its Diagnostic Correlation: a "High Avidity Result," which provides robust evidence of a past infection acquired more than four months prior. This is, in turn, correlated with the other primary finding of this meta-analysis—a High Specificity of 97%. This visual link powerfully communicates that the test is equally excellent at correctly identifying the established, high-avidity state, which is essential for reliably ruling out a recent infection and preventing unnecessary medical interventions.[16] By seamlessly integrating schematic representations of molecular interactions with the diagnostic interpretation and the high-level statistical findings of the study, this figure provides a sophisticated, multi-layered, and highly informative summary.

The exceptional performance of the IgG avidity test is a direct reflection of a fundamental and highly conserved process in adaptive immunology: the affinity maturation of the humoral immune response.[17] When a primary infection with *T. gondii* occurs, the host's immune system is presented with a novel set of parasitic antigens. The initial response involves the activation of naive B-cells, which differentiate into short-lived plasmablasts that secrete large quantities of IgM and, shortly thereafter, early IgG antibodies. This initial IgG repertoire is characterized by low avidity. The weak binding strength of these antibodies is a consequence of their germline-encoded variable regions, which have not yet been optimized for high-affinity antigen recognition. Our finding of a pooled sensitivity of 96% is a direct testament to the reliability of this early immunological signature. It indicates that in nearly all cases of a true acute infection, the dominant circulating IgG population will indeed exhibit low binding strength, making low avidity a highly sensitive marker for a recent encounter with the parasite. The few false-negative cases (a high-avidity result in a truly acute infection) are biologically plausible, potentially occurring in individuals who exhibit an unusually rapid avidity maturation process, though this is considered a rare phenomenon.[18] Conversely, the establishment of a chronic infection is immunologically defined by the generation of a long-lived, high-avidity antibody response. This is achieved through a meticulous process within the germinal centers of lymph nodes, where activated B-cells undergo somatic hypermutation, introducing random mutations into the genes encoding their antibody variable regions. B-cells that, by chance, acquire mutations leading to higher-affinity antibodies are preferentially selected for survival and expansion through interactions with follicular helper T-cells. This Darwinian-like selection process, unfolding over several months, culminates in the production of a highly specific and potent population of memory B-cells and long-lived plasma cells that secrete high-avidity IgG. Our finding of a pooled specificity of 97% powerfully validates this principle. It demonstrates that a high-avidity result is an extremely reliable indicator of an immune response that has undergone this maturation process, thus signifying an infection acquired in the distant past (typically more than four to five months prior). This makes high avidity a superb biomarker for excluding an acute infection during the current gestation, especially when testing is performed in the first trimester. The small number of false-positive cases (a low-avidity result in a chronic infection) may be explained by factors such as long-term persistence of a low-avidity subpopulation of

antibodies in some individuals or potential assay-specific artifacts.[19]

The derived likelihood ratios provide a practical translation of these immunological principles into clinical decision-making. The pooled Positive Likelihood Ratio (PLR) of 32.5 is exceptionally high. This means that a low-avidity result increases the pre-test odds of a patient having a true acute infection by more than 30-fold. In a clinical scenario where a pregnant woman has a 20% pre-test probability of acute infection based on her IgG/IgM profile, a low-avidity result would elevate her post-test probability to over 90%, effectively confirming the diagnosis and mandating clinical action. Similarly, the remarkably low pooled Negative Likelihood Ratio (NLR) of 0.04 provides immense reassurance. A high-avidity result reduces the pre-test odds of an acute infection by 96%. For the same patient with a 20% pre-test probability, a high-avidity result would decrease her post-test probability to less than 1%, effectively ruling out a gestational infection and averting the need for further invasive testing. The Diagnostic Odds Ratio (DOR) of 785 is a powerful, single metric that encapsulates this excellent discriminatory capacity. It represents the ratio of the odds of a positive test (low avidity) in a patient with acute infection to the odds of a positive test in a patient with chronic infection. A DOR of this magnitude signifies a test with an almost unparalleled ability to separate these two clinically distinct populations, positioning it as a definitive second-tier diagnostic test. The results of this meta-analysis have profound and immediate implications for the clinical management of pregnant women with suspected toxoplasmosis. The primary value of the IgG avidity test lies in its ability to bring clarity to the ambiguous IgG-positive/IgM-positive serological profile. Our data robustly support a management algorithm where a pregnant woman presenting with this profile before 16-20 weeks of gestation should immediately undergo IgG avidity testing. If the result shows high avidity, the clinician can, with a very high degree of confidence (underpinned by our 97% pooled specificity and 0.04 NLR), conclude that the infection was acquired before conception. This single piece of information effectively ends the diagnostic uncertainty. The patient can be reassured that her fetus is not at risk from congenital toxoplasmosis due to this infection. This avoids the significant psychological distress associated with a potential threat to the pregnancy, eliminates the need for serial follow-up serology, and, most importantly, prevents the unnecessary use of invasive procedures like amniocentesis. From a healthcare economics perspective, the routine application of avidity testing in this scenario is highly cost-effective, saving the substantial expenses associated with specialist consultations, advanced imaging, PCR testing, and unnecessary antimicrobial therapy.[20] If the result shows low avidity, the diagnosis of a primary infection acquired during or just prior to pregnancy is strongly supported (underpinned by our 96% pooled sensitivity and 32.5 PLR). This result is a clear signal for immediate clinical action. The patient should be thoroughly counseled regarding the risks of vertical transmission specific to her gestational age. Prenatal treatment, typically with spiramycin, should be initiated without delay to reduce the rate of placental transmission. The patient should also be referred for specialized fetal medicine consultation, where serial ultrasound monitoring for signs of fetal infection (ventriculomegaly, ascites, intracranial calcifications) can be performed. The option of amniocentesis for definitive PCR diagnosis of fetal infection should be discussed, as a positive result would prompt a switch in therapy to the more potent combination of pyrimethamine-sulfadiazine and folinic acid.

This evidence-based, two-step diagnostic pathway, guided by the IgG avidity test, represents a significant advancement over older practices that relied solely on ambiguous IgM results or complex interpretations of IgG titer kinetics. It provides a clear, efficient, and reliable framework for risk stratification, ensuring that interventions are targeted only to those who truly need them. The findings of our meta-analysis are broadly consistent with the conclusions of numerous individual studies and narrative reviews published over the past two decades, which have consistently

highlighted the value of avidity testing. However, by providing pooled, quantitative estimates, our study offers a higher level of evidence. The narrow confidence intervals around our summary estimates for sensitivity and specificity indicate that, despite some between-study variation, the overall performance of the test is consistently high. The substantial statistical heterogeneity observed (I^2 > 75%) is an important finding that warrants discussion. Rather than being a simple limitation, this heterogeneity reflects the real-world diversity of diagnostic platforms. The seven studies included in our analysis utilized assays from at least five different manufacturers. These commercial kits, while all based on the same avidity principle, differ in their specific antigenic preparations (recombinant vs. native antigens), the type and concentration of the denaturing agent used, incubation times, and the proprietary algorithms used to calculate the avidity index. This heterogeneity underscores a critical message for clinicians: it is essential to interpret avidity results strictly according to the manufacturer's instructions and validated cut-offs for that specific assay. It also highlights a major goal for the field of infectious disease diagnostics: the need for greater standardization and harmonization of avidity testing, perhaps through the development of international reference materials, to improve inter-laboratory comparability. While this study focused on providing a definitive answer on the test's accuracy, it is important to acknowledge that the clinical pathway is not always straightforward. The issue of "borderline" or "equivocal" avidity results was not uniformly addressed in the included studies and remains a challenge in practice. These intermediate results provide no definitive information and require further follow-up with repeat serology over two to three weeks to look for a significant rise in IgG titers or an evolution of the avidity index, thereby confirming or refuting a recent infection. Our analysis, by focusing on the clear low vs. high dichotomy, represents the test's performance in its most decisive applications.

5. Conclusion

This comprehensive meta-analysis provides unequivocal, high-level evidence that the IgG avidity test is a diagnostic tool of outstanding accuracy for differentiating acute from chronic *Toxoplasma gondii* infection in pregnant women. With a pooled sensitivity and specificity both exceeding 95% and a summary AUC of 0.99, its ability to discriminate between recent and past infections is exceptional. The immunological principles of antibody affinity maturation provide a robust biological foundation for this high performance. In clinical practice, the test serves as a powerful instrument for resolving the diagnostic uncertainty created by persistent IgM antibodies. A high-avidity result provides reliable reassurance and prevents unnecessary interventions, while a low-avidity result serves as a critical alert for the timely initiation of prenatal therapy and surveillance. The integration of IgG avidity testing into standard prenatal screening algorithms is a crucial, evidence-based strategy to improve maternal and fetal outcomes and is fundamental to the modern management of toxoplasmosis in pregnancy.

6. References

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